Organic Anion Transporter Gene Variants Associated With Plasma Exposure and Long-Term Response to Atrasentan in Patients With Diabetic Kidney Disease

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Plasma exposure of the endothelin receptor antagonist atrasentan varies between individuals and is associated with nephroprotective effects and the risk of heart failure. We examined the influence of genetic polymorphisms on atrasentan plasma exposure and pharmacodynamic effects. We performed a substudy of the Study of Diabetic Nephropathy With Atrasentan (SONAR) trial which enrolled adults with type 2 diabetes and chronic kidney disease (estimated glomerular filtration rate: 25–75 mL/min/1.73 m^2, and a urine albumin-to-creatinine ratio of 300–5,000 mg/g). Single nucleotide polymorphisms (SNPs) were determined for prespecified membrane transporters, metabolizing enzymes, and the endothelin-1 peptide. The associations among genotype, atrasentan plasma exposure, and the effect of atrasentan on the prespecified kidney and heart failure hospitalization (HHF) outcomes was assessed with Cox proportional hazards regression models. Of 3,668 patients randomized, 2,329 (63.5%) consented to genotype analysis. Two SNPs in the SLCO1B1 gene (rs4149056 and rs2306283), encoding the hepatic organic anion transporter 1B1 (OATP1B1), showed the strongest association with atrasentan plasma exposure. Based on their SLCO1B1 genotype, patients were classified into normal (atrasentan area under the plasma-concentration time curve from zero to infinity (AUC_{0-inf}) 41.3 ng·h/mL) or slow (atrasentan AUC_{0-inf} 49.7 ng·h/mL, $P < 0.001$) OATP1B1 transporter phenotypes. Among patients with a normal OATP1B1 phenotype, the hazard ratio (HR) with atrasentan for the primary kidney and HHF outcomes were 0.61 (95% confidence interval (CI): 0.45–0.81) and 1.35 (95% CI: 0.84–2.13), respectively. In the slow transporter phenotype, HRs for kidney and HHF outcomes were 1.95 (95% CI: 0.95–4.03, *P*-interaction normal phenotype = 0.004), and 4.18 (95% CI: 1.37–12.7, *P*-interaction normal phenotype = 0.060), respectively. OATP1B1 gene polymorphisms are associated with significant between-patient variability in atrasentan plasma exposure and long-term efficacy and safety.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The plasma exposure of the endothelin receptor antagonist atrasentan varies between individuals and is associated with nephroprotective effects and the risk of heart failure.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We examined the influence of genetic polymorphisms on atrasentan plasma exposure and pharmacodynamic (PD) effects in patients with type 2 diabetes and chronic kidney disease.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Based on their SLCO1B1 genotype, patients were classified into normal- or slow OATP1B1 transporter phenotypes. The slow OATP1B1 transporter phenotype group had a 20.3% higher atrasentan area under the plasma-concentration time curve from zero to infinity compared with the normal phenotype. Atrasentan compared with placebo slowed eGFR decline and reduced the risk of the primary kidney outcome in the normal OATP1B1 phenotype whereas this protective effect was absent in the slow OATP1B1 phenotype subgroup.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These data provide insight in genetic polymorphisms associated with pharmacokinetic and PD response variation to atrasentan and support the use of pharmacogenetics to tailor atrasentan treatment to those who may achieve maximal benefit with minimal side effects.

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The endothelin receptor antagonist atrasentan has been demonstrated to reduce the risk of kidney failure in carefully selected patients with type 2 diabetes and chronic kidney disease (CKD).[1] However, atrasentan may cause fluid retention in susceptible patients, which may lead to heart failure.[2] Previous studies showed a considerable variability between patients in the response to atrasentan which was, at least in part, explained by a similar variability in drug exposure.[3] This between-patient response variability to atrasentan determines the individual balance between benefits and risks of atrasentan.[4] Genetic polymorphisms may underly and contribute to the variability in atrasentan response. A better understanding of the genetic contribution to the between-patient variability in the pharmacokinetics (PKs) and pharmacodynamics (PDs) of atrasentan could aid in individualized therapy decisions.[5]

Several drug-transporters and enzymes have been previously investigated in relation to atrasentan metabolism and distribution: organic anion transporting polypeptides (OATP) transporters, P-glycoprotein (ABCB1), CYPP450 3A and UDP-glucuronosyltransferases (UGT).[6–8] Early healthy volunteer studies demonstrated that genetic variations in OATP, which are part of a large family of proteins involved in transport of endogenous compounds and xenobiotics, influence the disposition of atrasentan.[9] Patients with a slow transporter phenotype for OATP1B1 had a 73% higher plasma exposure compared with extensive transporter phenotypes.[8] A phase II study demonstrating that a single nucleotide polymorphism (SNP) in the *OATP1B1* gene (rs2306283) was associated with a lower atrasentan plasma exposure and attenuated reduction in albuminuria provided additional evidence for the involvement of genetic polymorphisms in atrasentan PKs and PDs.[10] However, the prior studies were of short duration and included a small number of subjects. In the Study of Diabetic Nephropathy With Atrasentan (SONAR) trial (NCT01858532), which investigated the long-term effects of atrasentan in adults with type 2 diabetes and CKD, genetic information was obtained for a large global cohort of patients.[1] This allowed us to investigate the influence of selected SNPs of membrane transporters, metabolizing enzymes, and target proteins relevant to the PKs and PDs of atrasentan on the atrasentan plasma exposure and response. The primary objective of this study was to evaluate the association between SNPs and atrasentan plasma exposure, and kidney and heart failure outcomes.

METHODS

Study design and patient population

This study is a *post hoc* analysis of the SONAR trial. The primary results, study design, and patient characteristics of the SONAR trial have been described previously.[1,11] The trial was designed and conducted in accordance with national regulatory and ethical guidelines. Inclusion criteria included age 18–85 years, presence of type 2 diabetes, an estimated glomerular filtration rate (eGFR) of 25–75 mL/min per 1.73 m^2, a urine albumin-to-creatinine ratio (UACR) of 300–5,000 mg/g, and brain natriuretic peptide (BNP) of no more than 200 pg/mL. Prior to randomization, all patients received 0.75 mg/day atrasentan open-label during a 6-week enrichment period, after which patients were identified as responder or nonresponder. Responders were defined as those with a ≥ 30% UACR reduction from baseline with no signs of fluid retention (defined as an increase in body weight ≥ 3 kg or increase in BNP ≥ 300 pg/mL). All patients were on a stable dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks prior to enrollment in the 6-week active open label phase. A total of 5,117 patients entered the enrichment period, of which 2,648 were identified as responders. After 6 weeks of enrichment, all responders and 1,020 nonresponders without overt signs of fluid retention were randomly assigned to continue 0.75 mg/day atrasentan or to transition to placebo. All patients who consented to genotyping prior to randomization were included in this study.

Selection of genetic polymorphisms

The DNA samples were analyzed with the Illumina – Infinium Global Screening array 24 version 3.[12] The Illumina array measured 640,909 genetic markers, including SNPs and copy number variants. For selection of relevant SNPs, we searched literature for transporters, enzymes, and drug targets potentially involved in the PKs and PDs of atrasentan. In addition to the OATP transporter family, we identified the P-glycoprotein (ABCB1), CYPP450 3A and UGT as possibly relevant to atrasentan distribution and metabolism.[6–8] The endothelin-1 (*EDN1*) and endothelin type-A (*EDRNA*) receptor genes were selected as direct drug targets for atrasentan.[13] Second, for the genes we investigated which SNPs may be relevant based on literature and the publicly available pharmacogenetics recourse PharmGKB (www.pharmgkb.org, last visited May 2021), which contains variant annotations with summaries of associations between SNPs and drug responses. We only selected SNPs with a minor allele frequency of at least 1%. Third, we assessed which of these SNPs were captured by the Illumina array.

The literature search resulted in the selection of 12 SNPs within 9 genes encoding for the following membrane transporters, metabolizing enzymes or drug targets: OATP1A2 (rs4148978),[8,14] OATP1B1 (rs2306283 and rs4149056),[8,15] OATP1B3 (rs4149117),[8,16] OATP2B1 (rs2306168),[17] ABCB1 (rs1128503),[8,18] CYP3A4 (rs35599367),[6,19] CYP3A5 (rs776746),[7] UGT1A1 (rs4148323 and rs887829),[8,20–22] and EDN1 (rs9296344 and rs5370).[23,24]

Prior studies showed key involvement of OATP1B1 transporters in the hepatic uptake of atrasentan. In analogy to a previous study, we combined two OATP1B1 transporter SLCO1B1 polymorphisms, rs2306283 and rs4149056, in order to classify patients into normal and slow OATP1B1 transporter phenotypes. To this end, we ranked all 9 possible SLCO1B1 genotypes based on their expected atrasentan plasma exposure, where we assumed that rs2306283 accelerates atrasentan hepatic uptake, whereas rs4149056 delays atrasentan hepatic uptake.[8,9,25–27] To increase study

power, we dichotomized and classified patients into two groups: the five SLCO1B1 genotypes expected to have the highest atrasentan plasma exposure were classified as slow transporter phenotype, whereas the remaining four SLCO1B1 genotypes were classified as normal transporter phenotype.

Atrasentan plasma exposure

Plasma samples were collected throughout the double-blind period at multiple study visits, predominantly prior to atrasentan administration. A previously developed population PK model was used to estimate atrasentan plasma exposure throughout the double-blind period of the trial.[3] In this model, the plasma concentration of atrasentan over time is described using patient characteristics, measured plasma concentrations, dose of atrasentan, and information about sampling and dosing times. The PK parameters of atrasentan, including volume of distribution and clearance, were estimated for the entire trial population. Subsequently, the individual deviation from the population mean parameters was derived for each patient. To this end, an individual estimate of the area under the plasma-concentration time curve (AUC), a measure that represents the overall plasma exposure of atrasentan, was derived from the model by dividing the dose of atrasentan by the individual's clearance as estimated by the model.

End points

The AUS from zero to infinity (AUC_{0-inf} (ng·h/mL)) was used as the PK end point. The primary composite kidney outcome of the SONAR trial, defined as the time from randomization to first occurrence of a sustained doubling of serum creatinine, time to end-stage kidney disease (defined as eGFR < 15 mL/min/1.73 m^2, need for chronic dialysis, and renal transplantation) or renal death was used as the PD end point. Time from randomization to first occurrence of heart failure hospitalization (HHF) was an additional clinical end point. The between-group difference in the rate of change in eGFR (eGFR slope) from randomization until the last treatment visit was an additional efficacy outcome. The change in BNP from randomization until the last treatment visit was selected as a surrogate outcome for fluid retention.

Statistics

Summary statistics were used to describe the demographic, physical, and clinical characteristics of patients included in the genetic analysis and the overall SONAR population. For each SNP genotype, we estimated the geometric mean of the atrasentan AUC_{0-inf} and 95% confidence interval (CI) of the geometric mean. The associations between SNPs and the natural logarithm of the atrasentan AUC_{0-inf} was assessed by linear regression, assuming an additive effect of allelic dosage. SNPs significantly associated with atrasentan plasma exposure were added to a multivariable linear regression model to estimate the explained variance of each covariate. Body weight and gender were included as covariates, as these factors were previously shown to be relevant for atrasentan plasma exposure.[3] The rs2306283 SNP was added to the model regardless of significance after inclusion of rs4149056, as the influence of rs2306283 may be masked by variation due to the rs4149056 SNP.[25] The statistical significance of the contribution of each SNP to a model consisting of clinical covariates was determined using analysis of variance, comparing models with- and without the addition of relevant SNPs. The percentage of variance explained was calculated using the difference in R^2 values between the models.

To determine the effect of atrasentan, the long-term kidney, and HHF outcomes, a Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and the 95% CI for the effect of atrasentan relative to placebo. Survival time to the first relevant outcome was used in each analysis. Patients were censored at their date of death, or for those who were alive at the end of follow-up, the date of their last clinic visit before the termination of the study. Treatment effects on the kidneys and HHF outcome were calculated according to the OATP1B1 phenotype. We added interaction terms (treatment * OATP1B1 phenotype) to the relevant Cox models to assess whether OATP1B1 phenotype modifies the treatment effect of atrasentan. Linear mixed effect models were used to assess the association between genotype and changes in eGFR slope and BNP. The BNP values were log transformed before analysis to take into account the skewed distribution. Treatment, genotype, visit, baseline value, and interactions between treatment and genotype and treatment and visit were included as fixed effects in the model, a random effect was included on the intercept. In an additional analysis, Fine and Gray competing risk regression was performed to take into account the competing risk of all-cause mortality. All analysis were performed with the software package R, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). The *survival* package (version 3.2–10) was used for the Cox proportional hazard model. For the linear mixed effect model the *nlme* package (version 3.1–152) was used.

RESULTS

Demographics

Of 3,668 patients randomly assigned to atrasentan or placebo, genetic data were available for 2,329 (63.5%) patients. Baseline characteristics between the overall SONAR cohort and genetic subgroup were similar (**Table 1**). The mean age was 64.9 years (SD: 8.5), 595 (25.5%) patients were female, mean eGFR was 43.3 mL/min per 1.73 m^2 (SD: 13.8), and median UACR was 861 mg/g (interquartile range: 490–1,566). Demographic, physical, and clinical characteristics at baseline were balanced between patients randomized to atrasentan and placebo (**Table 1**).

Pharmacokinetics

The geometric mean AUC_{0-inf} of atrasentan for all patients randomized to atrasentan (n = 1,137) was 42.4 ng·h/mL (95% CI: 41.0–43.9). There was a statistically significant trend in atrasentan plasma exposure across genotypes for rs4149056 (SLCO1B1), rs4148978 (SLCO1A2), rs2306168 (SLCO2B1), rs4148323 (UGT1A1), and rs5370 (EDN1; **Table 2**). The rs4149056, rs2306168, rs5370, and rs2306283 SNPs were significantly associated with atrasentan plasma exposure after stepwise addition in a linear regression model that included body weight and gender as fixed covariates. Body weight contributed most to the explained variance in AUC_{0-inf} with an R^2 of 7.2%, followed by rs4149056 (2.4%), rs2306283 (1.3%), gender (1.0%), rs230168 (0.5%), and rs5370 (0.4%). The rs4149056 and rs2306168 mutant alleles were associated with increased atrasentan plasma exposure, whereas rs2306283 and rs5370 were associated with decreased atrasentan plasma exposure. Patients homozygous for the rs4149056 mutation had a 42.3% higher AUC_{0-inf} compared with subjects homozygous for the wild-type (geometric mean 58.2 vs. 40.9 ng·h/mL).

Because the SLCO1B1-related SNPs showed the strongest association with atrasentan plasma exposure, we classified patients based on their SLCO1B1 genotype into normal or slow OATP1B1 transporters, in accordance with previous literature. There were 369 patients (15.9% of total study cohort, 175 assigned to atrasentan and 195 to placebo) with a slow transporter phenotype and 1,949 patients (84.1%; 976 assigned to atrasentan and 973 to placebo) with a normal OATP1B1 transporter phenotype. Patients with a slow OATP1B1 transporter phenotype were more often White persons and had a higher body weight (**Table S1**).

Table 1 Demographic data at the start of enrichment, including patients who consented to genetic analysis (stratified by treatment) and the general population enrolled in the double-blind phase

	Patients genotyped			
Characteristics	Atrasentan (*n* = 1,156)	Placebo (*n* = 1,173)	Total (*n* = 2,329)	Overall SONAR cohort (*n* = 3,668)
Age, years	65.1 (8.7)	64.9 (8.5)	65.0 (8.6)	64.5 (8.8)
Sex				
Women	291 (25.2%)	304 (25.9%)	595 (25.5%)	946 (25.8%)
Men	865 (74.8%)	869 (74.1%)	1734 (74.5%)	2,722 (74.2%)
Race				
White	714 (61.8%)	718 (61.2%)	1,432 (61.5%)	2,110 (57.5%)
Black	69 (6.0%)	81 (6.9%)	150 (6.4%)	224 (6.1%)
Asian	321 (27.8%)	323 (27.5%)	644 (27.7%)	1,198 (32.7%)
Other	52 (4.5%)	51 (4.3%)	103 (4.4%)	136 (3.7%)
Region				
Asia	166 (14.4%)	167 (14.2%)	333 (14.3%)	803 (21.9%)
Europe	402 (34.8%)	401 (34.2%)	803 (34.5%)	1,097 (29.9%)
Japan	144 (12.5%)	136 (11.6%)	280 (12.0%)	353 (9.6%)
Latin America	114 (9.9%)	109 (9.3%)	223 (9.6%)	426 (11.6%)
North America	330 (28.5%)	360 (30.7%)	690 (29.6%)	989 (27.0%)
Body weight, kg	86.5 (20.1)	86.7 (18.9)	86.6 (19.5)	30.3 (6.1)
BMI, kg/m^2	30.7 (6.2)	30.8 (5.8)	30.8 (6.0)	30.4 (6.3)
Duration of diabetes, years	16.6 (9.0)	17.0 (9.1)	16.8 (9.1)	16.5 (8.9)
Current smoker	192 (16.6%)	172 (14.7%)	364 (15.6%)	572 (15.6%)
Blood pressure				
Systolic, mmHg	137.0 (15.1)	136.2 (15.0)	136.6 (15.0)	136.2 (15.2)
Diastolic, mmHg	75.2 (9.8)	74.7 (9.9)	74.9 (9.8)	74.9 (9.9)
Serum creatinine, umol/L	147.8 (43.0)	150.6 (42.8)	149.2 (42.9)	149.7 (43.2)
eGFR, mL/min 1.73 m^2	43.8 (13.9)	42.8 (13.7)	43.3 (13.8)	43.3 (13.8)
Cholesterol				
LDL, mmol/L	2.4 (1.0)	2.5 (0.9)	2.5 (0.9)	2.5 (1.0)
HDL, mmol/L	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)	1.2 (0.4)
HbA1c, %	7.6 (1.4)	7.6 (1.5)	7.6 (1.5)	7.6 (1.5)
Serum albumin, g/L	39.1 (3.6)	39.0 (3.7)	39.0 (3.7)	39.1 (3.6)
UACR, mg/g	849 [482–1,542]	810 [457–1,486]	827 [463–1,520]	829 [458–1,556]
Responder	838 (72.5%)	843 (71.9%)	1,681 (72.2%)	2,648 (72.1%)
Hemoglobin, g/L	130.9 (17.5)	129.0 (17.3)	129.9 (17.4)	129.3 (17.1)
BNP, pg/mL	48 (26–86)	47 (26–86)	48 (26–86)	48 (26–87)
Diuretics prescribed	989 (85.6%)	988 (84.2%)	1977 (84.9%)	3,065 (83.6%)
Statin prescribed	918 (79.4%)	955 (81.4%)	1873 (80.4%)	2,913 (79.4%)

Count data is presented as: count (% of total). Normally distributed continues data is presented as: mean (SD). Not normally distributed continues data (UACR and BNP) are presented as: median [IQR].
BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SONAR, Study of Diabetic Nephropathy With Atrasentan; UACR, urine albumin creatinine ratio.

Atrasentan plasma exposure ranged from 38.7 ng·h/mL (95% CI: 35.9–41.7) to 76.4 ng·h/mL (95% CI: 57.0–102.3) depending on presence or absence of rs2306283 and rs4149056 mutations (**Table 3**). The 172 patients with available atrasentan PK data and a slow OATP1B1 phenotype had a geometric mean AUC_{0-inf} of 49.7 ng·h/mL (95% CI: 45.4–54.4) vs. 41.3 (95% CI: 39.8–42.8) for the 960 patients (84.8%) with the normal OATP1B1 phenotype (**Figure 1**).

Pharmacodynamics

In patients with a normal OATP1B1 phenotype, the kidney outcome occurred in 75 (7.7%) in the atrasentan group and 119

Table 2 Geometric mean of atrasentan AUC during the randomization phase per genotype: *P* values based on single variate linear regression model with log(AUC) as dependent variable

SNP	Genotype	*N*	Geometric mean AUC in ng·h/mL (95% CI)	*P* value
Transporters				
rs2306283 SLCO1B1	AA	247	42.9 (39.9–46.0)	0.327
	AG	508	43.2 (41.1–45.5)	
	GG	382	41.2 (38.8–43.6)	
rs4149056 SLCO1B1	CC	25	58.2 (47.2–71.7)	<0.001
	CT	274	46.2 (43.1–49.6)	
	TT	833	40.9 (39.3–42.5)	
rs4149117 SLCO1B3	GG	694	42.1 (40.3–43.9)	0.426
	GT	367	42.8 (40.3–45.4)	
	TT	75	44.4 (38.7–51.1)	
rs4148978 SLCO1A2	TT	105	37.5 (33.7–41.8)	0.039
	TC	487	42.4 (40.2–44.7)	
	CC	543	43.5 (41.4–45.6)	
rs2306168 SLCO2B1	CC	899	41.1 (39.6–42.7)	<0.001
	CT	209	47.6 (44.0–51.4)	
	TT	27	50.6 (42.0–60.9)	
rs1128503 ABCB1	GG	331	42.6 (40.1–45.4)	0.551
	GA	553	42.8 (40.8–45.0)	
	AA	252	41.3 (38.5–44.4)	
rs2231142 ABCG2	GG	825	41.8 (40.1–43.4)	0.197
	GT	266	44.6 (41.6–47.8)	
	TT	46	42.7 (35.7–50.9)	
Enzymes				
rs4148323 UGT1A1	GG	1,052	41.9 (40.4–43.4)	0.003
	GA	79	49.6 (43.8–56.1)	
	AA	5	64.1 (38.4–107)	
rs887829 UGT1A1	TT	113	42.2 (38.0–46.9)	0.959
	TC	423	42.7 (40.4–45.1)	
	CC	598	42.4 (40.4–44.4)	
rs35599367 CYP3A4	GG	1,083	42.7 (41.3–44.2)	0.148
	GA	51	36.8 (31.1–43.4)	
	AA	3	48.3 (36.7–63.6)	
rs776746 CYP3A5	CC	758	42.8 (41.0–44.6)	0.520
	CT	306	41.8 (39.3–44.5)	
	TT	72	41.5 (36.0–47.9)	
Endothelin-1				
rs9296344 EDN1	TT	998	42.5 (41.0–44.1)	0.576
	TC	128	42.2 (38.0–46.9)	
	CC	10	36.2 (23.2–56.6)	
rs5370 EDN1	GG	690	43.5 (41.7–45.4)	0.044
	GT	384	41.2 (38.8–43.7)	
	TT	63	38.5 (33.3–44.5)	

ABCB1, ATP-binding cassette sub-family B member 1; ABCG2, ATP-binding cassette super-family G member 2; AUC, area under the curve; CI, confidence interval; CYP, cytochrome P450; EDN1, endothelin-1 gene; SNP, short nucleotide polymorphism; SLCO1B1, solute carrier organic anion transporter gene; where final three characters describe specific SLCO gene; UGT1A1, UDP-glucuronosyltransferase 1 family; polypeptide A1.

Table 3 Atrasentan pharmacokinetics per SLCO1B1 genotype

SLCO1B1 genotype				
rs2306283 (c388A>G)	rs4149056 (c521T>C)	Number of patients (%)	Geometric mean AUC in ng·h/mL (95% CI)	Haplotype combinations
AA	CC	0 (0.0%)	NA	*5/*5
AG	CC	5 (0.4%)	76.4 (57–102.3)	*5/*15
GG	CC	20 (1.8%)	54.4 (42.6–69.4)	*15/*15
AA	TC	17 (1.5%)	48.8 (33.9–70.3)	*1A/*5
AG	TC	130 (11.5%)	48.3 (43.7–53.5)	*5/*1B and *1A/*15
GG	TC	127 (11.2%)	43.8 (39.7–48.4)	*1B/*15
AA	TT	229 (20.2%)	42.4 (39.5–45.6)	*1A/*1A
AG	TT	371 (32.8%)	41.4 (39.0–43.8)	*1A/*1B
GG	TT	233 (20.6%)	38.7 (35.9–41.7)	*1B/*1B
Slow OATP1B phenotype		172 (15.2%)	49.7 (45.4–54.4)	NA
Normal OATP1B1 phenotype		960 (84.8%)	41.3 (39.8–42.8)	NA
Complete study population		1,137 (100%)	42.4 (41.0–43.9)	NA

AUC, area under the curve; CI, confidence interval; NA, not applicable; OATP1B1, organic anion transporter polypeptide, where final three characters describe specific OATP transporter.
The rs2306283 SNP concerns an A to G substation (c.388A>G) and rs4149056 concerns a T to C substitution (c.521T>C). These two SNPs are in linkage disequilibrium and form 4 haplotypes: *1A (388A-521T), *1B (388G-521T), *5 (388A-521C), and *15 (388G-521C). Haplotypes are a set of genetic polymorphisms that tend to be inherited together due to their proximity on the same chromosome.

(12.2%) in the placebo group (HR: 0.61, 95% CI: 0.45–0.81; **Figures 1, 2**). Atrasentan did not reduce the risk of the kidney outcome in patients with a slow transporter phenotype (kidney outcomes in the atrasentan group 19 (10.9%) vs. placebo 12 (6.2%)); (HR: 1.95, 95% CI: 0.95–4.03, *P* interaction 0.004; **Figure 2**). The interaction between treatment and OATP1B1 genotype persisted in models adjusting for baseline age, sex, race, body weight, eGFR (*P* interaction 0.026). In patients with a normal OATP1B1 phenotype, the HHF occurred in 42 (4.3%) in the atrasentan group and 31 (3.2%) in the placebo group (HR: 1.35, 95% CI: 0.84–2.13, *P* = 0.219; **Figure 3**). In patients with a slow OATP1B1 phenotype, the HHF occurred in 14 (8.0%) in the atrasentan group and 4 (2.1%) in the placebo group (HR: 4.18, 95% CI: 1.37–12.7, *P* interaction 0.060; **Figure 3**). Adjusting the model for differences in patient characteristics between the slow and normal phenotype did not materially alter our findings (interaction *P* value between OATP1B1 genotype and treatment assignment 0.097). Within the atrasentan group, the unadjusted HRs for the slow vs. normal phenotype for the kidneys and HHF outcomes were 1.55 (95% CI: 0.93–2.56, *P* = 0.090) and 1.95 (95% CI: 1.06–3.57, *P* = 0.031), respectively. **Tables S3 and S4** show the effect of atrasentan compared with placebo on kidney and HHF outcomes for all genotypes. Results for both the composite kidney outcome and HHF were similar when accounting

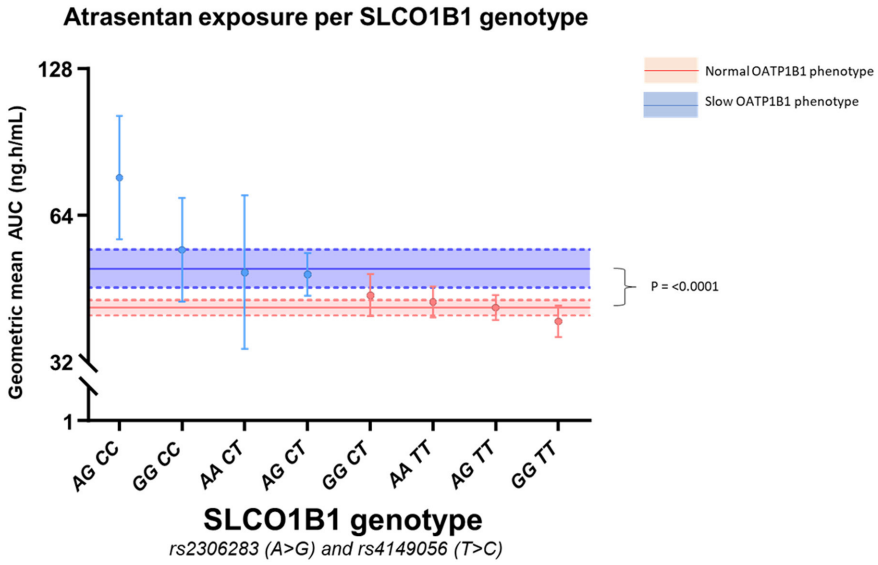

Figure 1 Geometric mean atrasentan AUC (ng·h/mL) per SLCO1B1 genotype and corresponding OATP1B1 phenotypes, error bars are 95% CIs. AUC, area under the plasma-concentration time curve; CIs, confidence intervals.

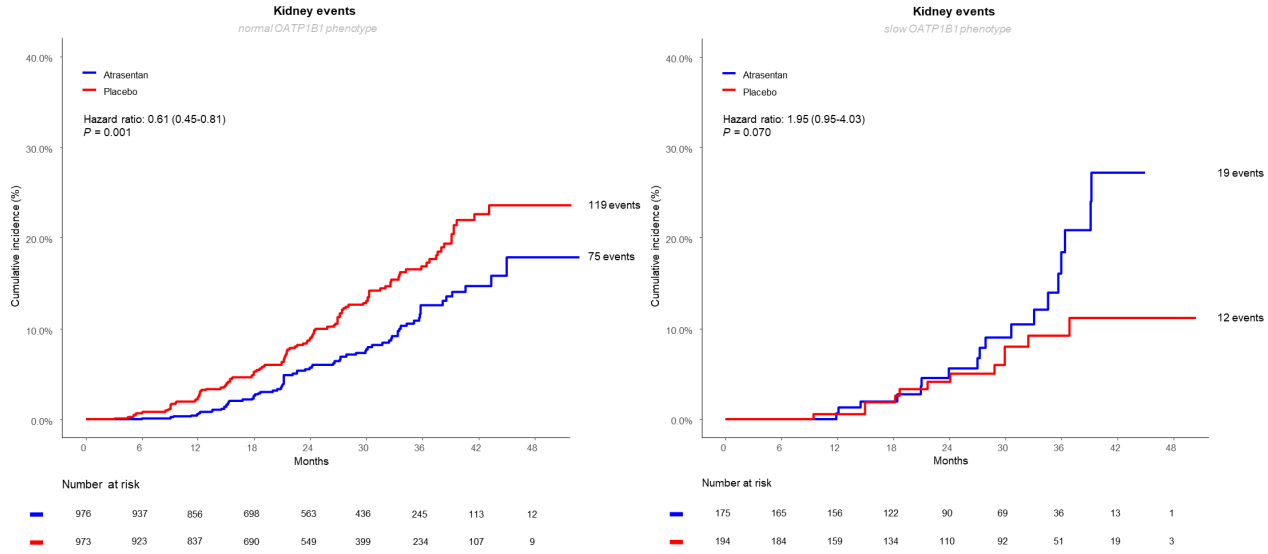

Figure 2 Effects of atrasentan on the primary composite kidney outcome in patients with normal and slow OATP1B1 phenotype.

for competing risk of mortality with Fine and Gray's proportional subdistribution hazards method with HR 0.60 (95% CI: 0.45–0.81, $P = 0.001$) in the normal phenotype and HR 1.93 (95% CI: 0.94–3.98, $P = 0.074$) in the slow phenotype for the kidney outcome. For the HHF end point, the respective HRs were 1.34 (95% CI: 0.84–2.13, $P = 0.218$) and HR 4.24 (95% CI: 1.42–12.59, $P = 0.009$; **Table S5**).

In patients with a normal OATP1B1 phenotype, annual eGFR decline was −2.7 mL/min/1.73 m^2 in the atrasentan group and −3.4 mL/min/1.73 m^2 in the placebo group (difference 0.7, 95% CI: 0.3–1.2; **Figure 4**). In patients with a slow phenotype, annual eGFR decline was −3.3 mL/min/1.73 m^2 in the atrasentan group and −3.4 mL/min/1.73 m^2 in the placebo group (difference 0.1, 95% CI: −1.2 to −1.0, P for interaction 0.261; **Figure 4**).

Among patients with the normal OATP1B1 phenotype, the BNP levels were 3.9% (95% CI: 0.4–7.4) larger in the atrasentan group compared with the placebo group. In patients with the slow OATP1B1 phenotype, the difference in BNP between atrasentan and placebo was 11.6% (95% CI: 3.5–19.8, P for interaction < 0.001).

DISCUSSION

Based on a large double-blind placebo-controlled trial determining the protective effects of atrasentan vs. placebo on major kidney outcomes, we demonstrated that genetic polymorphisms in genes encoding organic anion transporters involved in the uptake of atrasentan in hepatocytes are associated with a higher atrasentan plasma exposure compared with patients with the wild-type variants in these genes. When classifying patients in a normal or slow organic anion

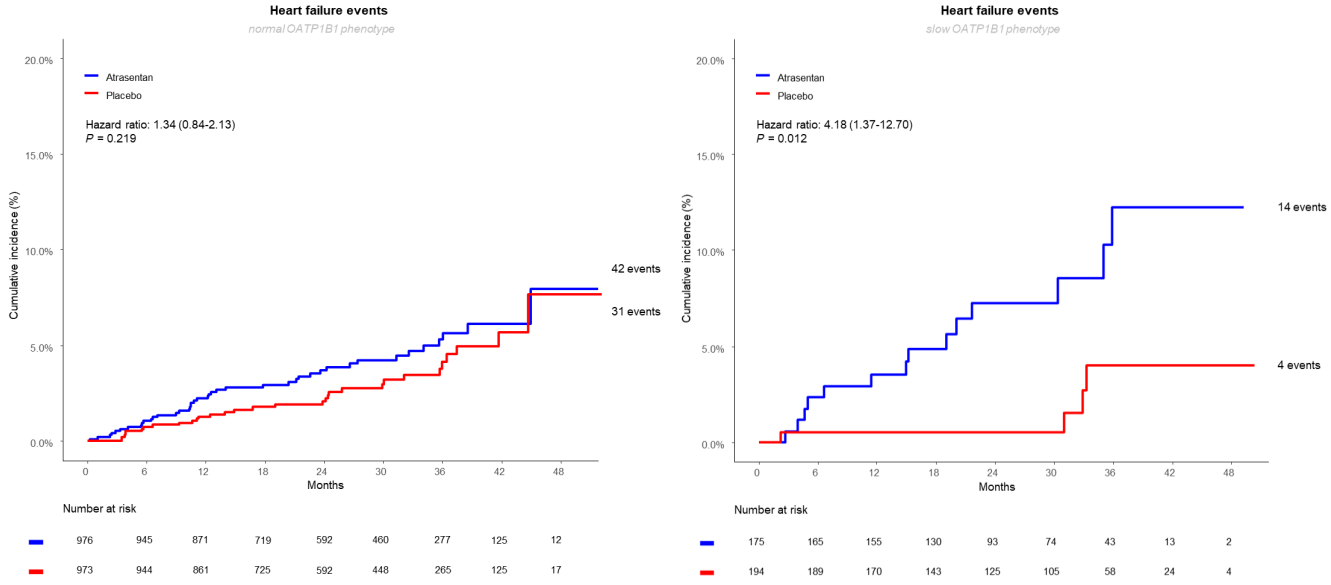

Figure 3 Effects of atrasentan on the hospitalization for heart failure in patients with normal and slow OATP1B1 phenotype.

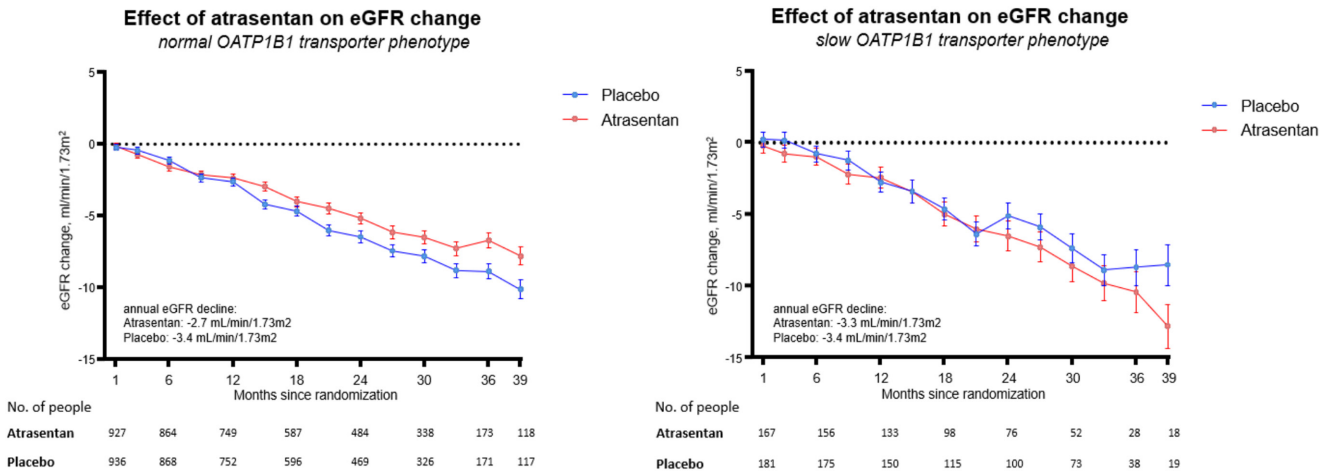

Figure 4 Effects of atrasentan on the change in estimated glomerular filtration rate (eGFR) in patients with normal and slow OATP1B1 phenotype.

transporter phenotype, atrasentan compared with placebo slowed eGFR decline and reduced the risk of the primary kidney outcome in the normal OATP1B1 phenotype whereas this protective effect was absent in the slow OATP1B1 phenotype subgroup. In addition, atrasentan tended to increase the risk of HF hospitalization in the slow compared with the normal phenotype subgroup. These data provide insight in underlying genetic polymorphisms associated with individual PK and PD response variation to atrasentan and support the use of pharmacogenetics to tailor atrasentan treatment to those who may achieve maximal benefit with minimal side effects.

Previous studies in healthy volunteers and patients with type 2 diabetes have demonstrated a large between-patient variability in atrasentan plasma exposure which is associated with a similar inter-individual variability response in UACR and body weight as proxies of kidney protection and fluid retention. Atrasentan is metabolized to inactive metabolites in the liver.[6,8] Transport of atrasentan into hepatocytes is facilitated by OATP influx transporters expressed on sinusoidal membranes of hepatocytes. A healthy volunteer study demonstrated that carriers of a SLCO1B1 polymorphism (rs4149056), encoding OATP1B1, had significantly higher atrasentan plasma exposure compared with subjects carrying the wild-type variant.[8] Additionally, the rs2306283 SNP in the *SLCO1B1* gene was associated with lower atrasentan plasma exposure and a diminished reduction in albuminuria in an atrasentan phase II study in patients with type 2 diabetes and CKD.[10] The previous studies were small and often included healthy volunteers. Our study confirms and extend these findings to a large well-characterized contemporary global cohort of patients with type 2 diabetes and CKD by demonstrating that common polymorphisms of the OATP1B1 hepatic uptake transporter are associated with significant alterations in atrasentan plasma exposure. Despite considerable variability in plasma exposure within each SLCO1B1 genotype, there was a clear trend in higher atrasentan plasma exposure with reduced hepatic uptake for the rarer variant SLCO1B1 genotypes. Specifically, comparing patients with the *5/*15 diplotype compared with the *1B/*1B diplotype—the most divergent genotypes in terms of expected OATP1B1 transporter activity—we observed a 97% increase in atrasentan plasma exposure.

In addition to variability in PKs, prior studies also reported considerable variability in kidney- and heart failure outcomes during treatment with atrasentan. Koomen *et al*. demonstrated that increased atrasentan plasma exposure was associated with a decrease in kidney events and increase in heart failure events.[28] However, in that study, the factors underlying the variation in PD outcomes were not investigated. We observed an association among the OATP1B1 transporter phenotype, plasma exposure, and clinically relevant long-term outcomes. The kidney protective effects of atrasentan as observed in the overall SONAR population were not present among patients with a slow OATP1B1 transporter phenotype whereas atrasentan tended to increase the risk of heart failure hospitalization in this subgroup. Although the number of events was small, these results suggest a potentially adverse risk–benefit profile of atrasentan for patients with the slow OATP1B1 transporter phenotype, and are clinically important because approximately one out of six patients was classified with a slow transporter phenotype.

We do not know why the higher exposure does not translate into increased kidney protection among slow transporters. A previous *post hoc* analysis from SONAR reported that a higher atrasentan exposure was, on average, associated with a more pronounced reduction in the risks of kidney outcomes.[4] However, we now show that in some patients with a higher exposure, atrasentan is not associated with increased kidney protection. Because of the bidirectional relationship between heart failure and kidney failure it is possible that increased sodium retention during high exposure to atrasentan leads to edema and heart failure which may in turn accelerate kidney function decline. In particular, fluid congestion could induce increased renal interstitial pressure within the rigid capsule of the kidney with secondary compression of kidney tissue which could contribute to reduced kidney function.[28] An alternative explanation may be that increased sodium retention due to atrasentan reduces the kidney protective effects of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which were used per protocol by all patients in the SONAR trial.[29]

There is considerable genetic variation of SLCO1B1 polymorphisms among different races, with higher frequencies of the rs4149056 mutation among people from European descent (18%) and lower frequencies among people from sub-Saharan Africa

(1.9%).[15] Accordingly, slow transporters were primarily White persons (81.0%), whereas normal transporters were more often Asian (30.4%) and Black persons (7.3%). The larger proportion of White persons among slow OATP1B1 transporters may explain the higher body weight in this group.

In addition to the association between SLCO1B1 polymorphisms and atrasentan plasma exposure, we found that atrasentan plasma exposure significantly varied across two other genetic polymorphisms after adjustment for age and sex: rs2306168 in the *SLCO2B1* gene and rs5370 in the *EDN1* gene. The *SLCO2B1* gene encodes the OATP2B1 transporter protein, which is not only expressed in hepatocytes, but also in the intestines, placenta, heart, and skin.[30] Interaction studies between SLCO2B1 and atrasentan have not been undertaken but it is possible that the rs2306168 SNP may influence the hepatic uptake of atrasentan. The precise mechanisms for how EDN1 polymorphisms affect atrasentan plasma exposure are unknown but receptor mediated absorption, which has been demonstrated for endothelin receptor antagonists before, may be involved.[31]

This study has several limitations. The population in this *post hoc* study excluded participants with signs of fluid retention during the open-label enrichment phase. We cannot determine to what extent patients with a slow OATP1B1 phenotype were excluded because DNA was only collected in randomized participants. Second, we have assumed that additional effects of two mutation alleles occur linearly but cannot exclude the possibility of nonlinear additive effects. As the number of publications on the pharmacogenomics of atrasentan was limited, we analyzed a small set of SNPs. It is possible that other unmeasured polymorphisms also contribute to variation in atrasentan PKs and PDs. The OATP1B1 slow phenotype was a small population with relatively few clinical events during follow-up increasing the possibility of chance findings. However, the different effects of atrasentan in the normal and slow OATP1B1 phenotypes were consistent when analyzing the continuous surrogate outcomes eGFR slope and BNP changes making the possibility of chance findings less likely. Finally, we did not correct for multiple testing in the statistical analysis.

In conclusion, this study demonstrated associations among polymorphisms of *SLCO1B1*, *SLCO2B1*, and *EDN1* and atrasentan plasma exposure. Patients with a slow OATP1B1 transporter phenotype were exposed to significantly higher plasma levels of atrasentan. Importantly, in these patients, atrasentan did not confer nephroprotection and tended to increase the risk of hospital admissions due to heart failure.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

D.H.K. has served as a consultant for AbbVie, AstraZeneca, Chinook Therapeutics, and Travere Therpeutics. J.J.V.M. has received payments through Glasgow University from work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos Personal lecture fees: the Corpus, Abbott, Hikma, Sun Pharmaceuticals, Medscape/Heart.Org, Radcliffe Cardiology, Servier Director, and Global Clinical Trial Partners (GCTP). G.B. reports support from T32 NIH grant DK07011 and is a consultant to: Merck, Bayer, KBP Biosciences, Ionis, Alnylam, Astra Zeneca, Quantum Genomics, Horizon, and Novo Nordisk, and steering committee of trials-Bayer, Quantum Genomics, Alnylam, and Novo Nordisk. R.C.R. serves on advisory boards for Boehringer and AstraZeneca and has been a speaker for AstraZeneca, Boehringer Ingelheim, AbbVie, Takeda, Amgen, and Janssen. F.F.H. has served as a consultant for and received honoraria from AbbVie and AstraZeneca. D.W.K. reported grant funding from Novartis, Bayer, Novo Nordisk, and Astra Zeneca; honoraria for consulting from AbbVie, Bayer, Merck, Medtronic, Relypsa, Merck, Corvia Medical, Boehringer-Ingelheim, Novo Nordisk, Astra Zeneca, Keyto, Pfizer, and Novartis; stock ownership in Gilead Sciences. H.M. has served on steering committees for AbbVie and Teijin and on advisory boards for Boehringer Ingelheim and Travere Therapeutics. M.N. is the speaker honoraria and participation in Advisory Boards: Sanofi, Takeda, Amicus, Pfizer, Astellas, Swiss Pharma, Travere Therapeutics, and AstraZeneca. Travel grants: Sanofi, Amicus, Takeda, AstraZeneca. V.P. has served on Steering Committees for trials funded by AbbVie, Boehringer Ingelheim, GSK, Janssen, Novo Nordisk, Retrophin, and Tricida; and has participated in scientific presentations or advisory boards with AbbVie, Astellas, AstraZeneca, Bayer, Baxter, BristolMyers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, and Tricida. P.R. has received research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Astellas, AbbVie, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi, and Vifor; all fees are given to Steno Diabetes Center Copenhagen. S.T. participates on a steering committee for Bayer Fidelio/Figaro studies, and speaker's bureau with Servier and Pfizer. H.H.P. was the cochair of the SONAR study steering committee and serves as a consultant for AbbVie. D.d.Z. served on advisory boards and/or speaker for Bayer, Boehringer Ingelheim, Fresenius, Mitsubishi-Tanabe, Travere Pharmaceuticals; Steering Committees and/or speaker for AbbVie and Janssen; Data Safety and Monitoring Committees for Bayer. Honoraria paid to Institution and consultant/speaker. H.J.L.H. is supported by a VIDI (917.15.306) grant from the Netherlands Organisation for Scientific Research and has served as a consultant for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe, and Retrophin; and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.D.S., J.V.K., and H.J.L.H. wrote the manuscript. D.E.K., J.J.V.M., G.L.B., R.C.R., F.F.H., D.W.K., H.K., G.M., M.N., V.P., P.R., S.T., H.H.P., D.d.Z., and H.J.L.H. designed the research. All authors performed the research. J.D.S., J.V.K., and H.J.L.H. analyzed the data.

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